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# Predictors and outcomes of neoatherosclerosis in patients with in-stent restenosis

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**KEYWORDS**

- drug-eluting balloon
- in-stent restenosis
- optical coherence tomography

## Abstract

**Background:** In-stent restenosis (ISR), especially for neoatherosclerosis, is still a major problem of percutaneous coronary intervention (PCI) even in the drug-eluting stent (DES) era.

**Aims:** The purpose of this study was to investigate the impact of neoatherosclerosis on prognosis after PCI for ISR.

**Methods:** Between March 2009 and December 2017, 313 ISR lesions in patients undergoing an OCT-guided PCI in five hospitals were retrospectively enrolled. Neoatherosclerosis was defined as a lipid neointima or calcified neointima. We examined the association between neoatherosclerosis and the clinically driven target lesion revascularisation (CD-TLR) rates.

**Results:** In 313 ISR lesions, 64 lesions (20.4%) had bare metal stents and 241 lesions (77.0%) had drug-eluting stents (DES). Among them, 47.0% of lesions (147 lesions) had neoatherosclerosis. A multivariate logistic regression analysis demonstrated that eGFR (odds ratio [OR] 0.986, 95% confidence interval [CI]: 0.974-0.998; p=0.023), the time from PCI to the ISR (OR 1.13, 95% CI: 1.06-1.22; p<0.001) and DES-ISR (OR 2.48, 95% CI: 1.18-5.43; p=0.019) were independent predictors for neoatherosclerosis. A multivariate regression analysis demonstrated that neoatherosclerosis was an independent predictor of CD-TLR.

**Conclusions:** In this multicentre ISR registry, OCT imaging demonstrated that eGFR, the time from PCI to the ISR and DES-ISR were independent predictors for neoatherosclerosis and that neoatherosclerosis in ISR lesions had a worse impact on the CD-TLR rate.

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## Abbreviations

| | |
|---|---|
| **BMS** | bare metal stent(s) |
| **CD-TLR** | clinically driven target lesion revascularisation |
| **DCB** | drug-coated balloon(s) |
| **DES** | drug-eluting stent(s) |
| **eGFR** | estimated glomerular filtration rate |
| **ISR** | in-stent restenosis |
| **LDL** | low-density lipoprotein |
| **MLD** | minimum lumen diameter |
| **OCT** | optical coherence tomography |
| **PCI** | percutaneous coronary intervention |
| **POBA** | plain old balloon angioplasty |
| **QCA** | quantitative coronary angiography |
| **TCFA** | thin-cap fibroatheroma |

## Introduction

Drug-eluting stents (DES) have demonstrated superiority over bare metal stents (BMS). This has led to the near elimination of BMS from routine clinical practice[1,2]. However, in-stent restenosis (ISR) is still a major problem of percutaneous coronary intervention (PCI), especially for neoatherosclerosis, even in the DES era[3]. In fact, despite the better clinical outcomes with new-generation durable polymer DES, a pathological study demonstrated that the frequency of neoatherosclerosis was similar between the newer- and first-generation DES[4]. Moreover, a pathological study showed that neoatherosclerosis was associated with ISR in both BMS and DES implantation and it has been consistently correlated with late thrombotic events post stent implantation[4]. On the other hand, an assessment of the neointimal characteristics, especially of neoatherosclerosis, using optical coherence tomography (OCT), is important for clarifying the pathophysiology of ISR lesions. A few reports demonstrated the impact of neoatherosclerosis on clinical outcome[5,6], though there are no data on the influence of neoatherosclerosis after PCI to the ISR. The purpose of this study was to investigate the influence of neoatherosclerosis on clinical outcome using plain old balloon angioplasty (POBA), DES and drug-coated balloons (DCB).

## Methods

### PATIENT POPULATION

This study was a multicentre, retrospective observational study. Between March 2009 and December 2017, ISR lesions undergoing an OCT-guided PCI in five different hospitals in Japan were retrospectively enrolled. The study exclusion criteria were haemodynamic instability, age less than 18 years, and a life expectancy of less than six months due to a non-cardiac condition. After excluding cases with incomplete OCT data and poor OCT quality, 313 ISR lesions in 311 patients were enrolled. This study was approved by the institutional review board of each participating institution with a waiver of the requirement for informed consent.

### QUANTITATIVE CORONARY ANALYSES

Detailed methods are provided in **Supplementary Appendix 1**.

### OCT IMAGE ACQUISITION

Detailed methods are provided in **Supplementary Appendix 2**.

### OCT IMAGE ANALYSIS

The OCT analyses were performed using dedicated software with an automated contour-detection algorithm (Off-line Review Software, version E.0.2; Abbott Vascular, Santa Clara, CA, USA). All cross-sectional images were initially screened by a quality assessment and excluded from the analysis if any portion of the stent was out of the screen, a side branch occupied >45% of the cross-section, or the image was of poor quality caused by residual blood, artefact, or reverberations. A qualitative image assessment was performed for every frame, whereas quantitative measurements were performed every 1 mm along the entire stented segment. For the morphometric analysis, the standard definitions of the cross-sectional area measurement were applied as previously reported[7]. The stent, lumen, and neointimal hyperplasia cross-sectional areas were measured at 1.0 mm axial increments throughout the entire length of the stent. The proximal and distal references were measured at the site with the largest lumen within 5 mm proximal and distal to the stented segment. The neointima was defined as the tissue between the luminal contour and stent contour and estimated in all frames in the stent. A homogenous neointima was identified as having signal-rich regions with low attenuation. A calcified neointima had a well-delineated, signal-poor region with sharp borders. A lipid neointima was defined as having signal-poor regions with diffuse borders and a high attenuation[8]. Neoatherosclerosis was defined as a lipid or calcified neointima **(Figure 1)**[8]. In the lipid neointimas, the fibrous cap thickness was

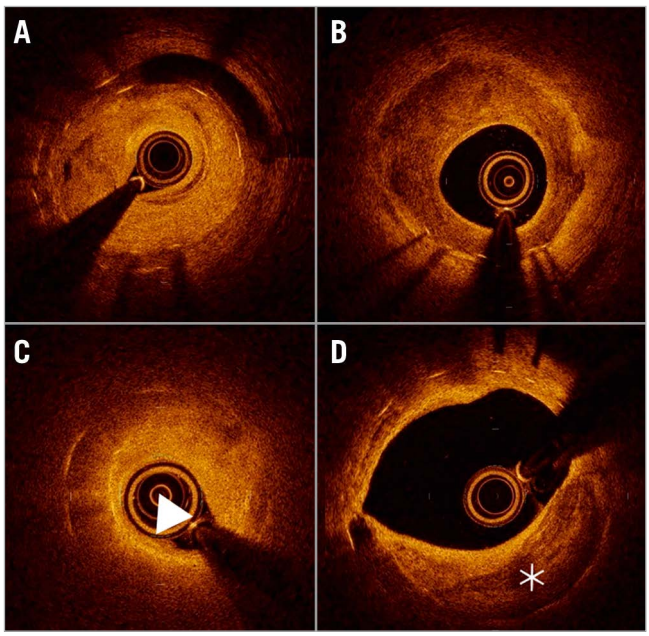


**Figure 1.** *Representative optical coherence tomography image. A) Homogenous neointima. B) Heterogenous neointima. C) Lipid neointima (arrow). D) Calcified neointima (asterisk).*

computed as the mean of three evenly distributed measurements along the fibrous cap[8]. A thin-cap fibroatheroma (TCFA) neointima was defined as a lipid neointima with a fibrous cap thickness of ≤65 µm at the thinnest part. Inter- and intra-observer variabilities were k=0.93 and k=0.93 for neoatherosclerosis, k=0.93 and k=0.86 for lipid neointima, and k=0.81 and k=0.81 for calcified neointima.

### OUTCOME MEASURES

The clinical outcome data were obtained by reviewing the outpatient records for death, myocardial infarction, and target lesion revascularisation (TLR). The primary outcome was clinically driven target lesion revascularisation (CD-TLR). CD-TLR was defined as any revascularisation procedure of the target lesion in the presence of angiographic restenosis and signs or symptoms of ischaemia[9]. The secondary outcomes were CD-TLR in the DCB cohort, all-cause death, cardiac death, and target vessel myocardial infarction in the entire cohort.

### STATISTICAL ANALYSIS

Data are presented as values and percentages, means±SD, or medians and interquartile ranges (IQR; Q1, Q3). Continuous variables were compared between the groups using the unpaired t-test or Mann-Whitney U test, based on the data distribution. Categorical variables were compared between the two groups with the chi-square test or Fisher's exact test, as appropriate. Multiple lesions within the same patient were assumed to be independent of each other. First, multivariate logistic regression analysis was performed to determine the association of baseline characteristics with neoatherosclerosis. Age, sex, hypertension, current smoking, diabetes and haemoglobin A1c levels >7.0%, estimated glomerular filtration rate (eGFR, 1 mL/min/1.73 m$^2$), >70 mg/dL of low-density lipoprotein (LDL) cholesterol, type of previous stent (BMS or DES), stent length and neointimal thickness were chosen as variables according to a previous report[10]. Results of the model are presented as the odds ratio (OR) and 95% confidence interval (CI).

Subsequently, the Kaplan-Meier method was used to estimate the cumulative probability of freedom from CD-TLR. A multivariable Cox proportional hazards regression model was used to evaluate the effect of neoatherosclerosis while adjusting for covariates including age, sex, current smoking, diabetes, eGFR (1 mL/min/1.73 m$^2$), LDL cholesterol, type of previous stent, lesion length, and PCI strategy (POBA, or DES implantation). Results of the model are presented as the hazard ratio (HR) and 95% CI. Since a CD-TLR is a recurrent event, the Prentice, Williams and Peterson gap time (PWP-GT) model was also used to estimate the effect of neoatherosclerosis on CD-TLR while controlling for the above covariates[11]. The above analyses were also performed in the DCB cohort. All tests were two-sided with a 5% significance level. The statistical analyses were performed with R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

## Results

### CLINICAL, LESION CHARACTERISTICS AND QCA

A total of 313 lesions (311 patients) with ISR were included **(Figure 2)**. The baseline patient and lesion characteristics are shown in **Table 1** and **Table 2**. In 313 ISR lesions, 64 lesions (20.4%) had bare metal stents and 241 lesions (77.0%) had drug-eluting stents (DES). Among 241 DES, 73 lesions had first-generation DES and 168 lesions had new-generation DES. In terms of the treatment strategy, DCB was performed in 62.2% of lesions, while DES were implanted in 16.7% of lesions.

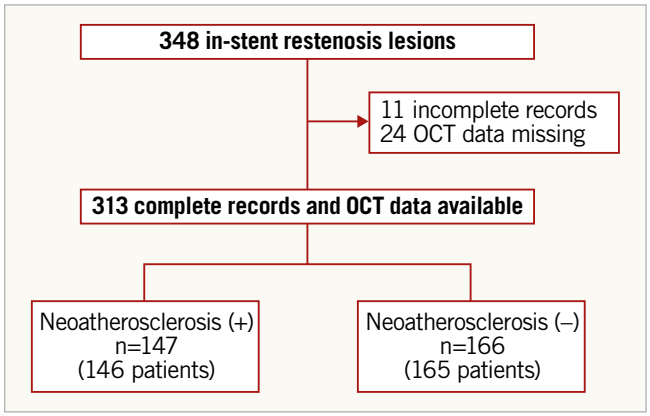


**Figure 2.** *Flow diagram of the study. DCB: drug-coated balloon; DES: drug-eluting stent; OCT: optical coherence tomography; POBA: plain old balloon angioplasty*

One hundred and forty-seven lesions (47%) had neoatherosclerosis in all lesions. Patients with neoatherosclerosis were significantly older compared to those without neoatherosclerosis (71.3±8.4 vs 69.0±10.1 years, p=0.035). The eGFR was significantly lower in the lesions with neoatherosclerosis (56.6 [25.0-70.4] vs 61.0 [46.3-73.9], p=0.016). The LDL-cholesterol level was higher in the neoatherosclerosis group, though it did not reach statistical significance (94.9±28.7 vs 90.2±27.1 mg/dl, p=0.141). The time from the index stent implantation to the ISR was significantly longer in the lesions with neoatherosclerosis (1,391 [389-3,274] vs 661 [294-1,688] days, p<0.001). The QCA analysis demonstrated that the post-PCI MLD and acute gain were significantly smaller in the neoatherosclerosis group **(Table 3)**.

### OCT FINDINGS

Details of the OCT findings are shown in **Table 3**. There were no significant differences in the minimum lumen area, stent area, and neointima area between the two groups. The proximal reference area was significantly greater in the lesions with neoatherosclerosis than in those without neoatherosclerosis. Lipid neointima and calcified neointima were detected in 93.2% and 23.8% of the lesions with neoatherosclerosis, respectively **(Table 3)**. The minimum fibrous cap thickness and percentage of frames (longitudinal extension) with neoatherosclerosis in the entire stent segment were 117.3±64.2 µm and 13.5 [7.5-27.6] %, respectively.

**Table 1. Patient characteristics.**

| | Overall N=311 | Neoatherosclerosis + N=146 | Neoatherosclerosis – N=165 | *p*-value |
|---|---|---|---|---|
| Age, years | 70.1±9.4 | 71.3±8.4 | 69.0±10.1 | 0.035 |
| Male | 249 (80.1) | 116 (79.6) | 133 (80.6) | 0.914 |
| Body mass index | 23.9±3.7 | 23.8±3.8 | 23.9±3.5 | 0.849 |
| Smoking | 143 (46.1) | 67 (45.9) | 76 (46.3) | >0.999 |
| Hypertension | 261 (84.2) | 124 (84.9) | 137 (83.5) | 0.744 |
| Diabetes mellitus | 177 (56.9) | 86 (58.9) | 91 (55.1) | 0.578 |
| Dyslipidaemia | 216 (69.5) | 97 (66.4) | 119 (72.1) | 0.402 |
| Stroke | 29 (9.4) | 12 (8.2) | 17 (10.4) | 0.650 |
| Atrial fibrillation | 29 (9.4) | 14 (9.7) | 15 (9.3) | >0.999 |
| History of CABG | 15 (4.8) | 8 (5.5) | 7 (4.3) | 0.819 |
| **Laboratory finding** | | | | |
| Haemoglobin, g/dl | 12.8±1.7 | 12.7±1.8 | 12.9±1.7 | 0.265 |
| eGFR, mL/min/1.73 m$^2$ | 59.7 [41.0-72.8] | 56.6 [25.0-70.4] | 61.0 [46.3-73.9] | 0.016 |
| HbA1c, % | 6.45±1.11 | 6.48±1.24 | 6.42±0.99 | 0.610 |
| LDL cholesterol, mg/dl | 92.4±27.9 | 94.9±28.7 | 90.2±27.1 | 0.141 |
| Triglyceride, mg/dl | 120.0 [84.0-167.8] | 113.0 [83.0-160.0] | 125.0 [86.0-172.5] | 0.392 |
| **Medication** | | | | |
| Aspirin | 305 (98.1) | 143 (97.9) | 162 (98.2) | >0.999 |
| P2Y$_{12}$ inhibitor | 289 (92.9) | 136 (93.2) | 153 (92.7) | >0.999 |
| Anticoagulant | 33 (10.6) | 14 (9.6) | 19 (11.5) | 0.713 |
| Statin | 247 (79.4) | 113 (77.4) | 134 (81.2) | 0.051 |

**Table 2. Lesion and procedural characteristics.**

| | | Overall N=313 | Neoatherosclerosis + N=147 | Neoatherosclerosis – N=166 | *p*-value |
|---|---|---|---|---|---|
| Time from PCI to the ISR, days | | 732 [348-2,553] | 1,391 [389-3,274] | 661 [294-1,688] | <0.001 |
| Stent number, n | | 1.0 [1.0-1.0] | 1.0 [1.0-2.0] | 1.0 [1.0-1.0] | 0.451 |
| Stent length, mm | | 30.8±16.9 | 30.7±15.1 | 30.9±18.3 | 0.926 |
| Stent diameter, mm | | 2.96±0.40 | 2.98±0.41 | 2.95±0.40 | 0.664 |
| Lesion location | Left anterior descending | 154 (49.2) | 76 (51.7) | 78 (47.0) | 0.659 |
| | Right coronary artery | 105 (33.5) | 48 (32.7) | 57 (34.3) | |
| | Left circumflex | 54 (17.3) | 23 (15.6) | 31 (18.7) | |
| Type of previous stent | Bare metal stent | 64 (20.4) | 25 (17.0) | 39 (23.5) | 0.364 |
| | Drug-eluting stent | 241 (77.0) | 118 (80.3) | 123 (74.1) | |
| | First-generation | 73 (23.3) | 44 (29.9) | 29 (17.5) | |
| | New-generation | 168 (53.7) | 74 (50.3) | 94 (56.6) | |
| | Unknown | 8 (2.6) | 4 (2.7) | 4 (2.4) | |
| Final strategy | POBA | 66 (21.2) | 26 (17.7) | 40 (24.2) | 0.265 |
| | DCB | 194 (62.2) | 98 (66.7) | 96 (58.2) | |
| | DES | 52 (16.7) | 23 (15.6) | 29 (17.6) | |
| ELCA | | 64 (20.6) | 28 (19.0) | 36 (22.1) | 0.603 |
| Quantitative coronary angiography | Lesion length, mm | 16.9±12.3 | 17.1±12.7 | 16.8±12.0 | 0.867 |
| | Reference vessel diameter, mm | 2.67±0.50 | 2.66±0.53 | 2.67±0.47 | 0.923 |
| | Pre MLD, mm$^2$ | 0.64±0.40 | 0.66±0.37 | 0.63±0.43 | 0.436 |
| | Pre percent diameter stenosis, % | 77.0±14.8 | 75.8±14.3 | 78.1±15.2 | 0.174 |
| | Post MLD, mm$^2$ | 2.15±0.49 | 2.09±0.49 | 2.21±0.48 | 0.030 |
| | Post percent diameter stenosis, % | 23.0±13.5 | 25.0±13.4 | 21.2±13.3 | 0.014 |
| | Acute gain | 1.59±1.17 | 1.48±0.92 | 1.68±1.35 | 0.013 |

**Table 3. Optical coherence tomography findings.**

| | | Overall N=313 | Neoatherosclerosis + N=147 | Neoatherosclerosis – N=166 | *p*-value |
|---|---|---|---|---|---|
| Minimum lumen area, mm² | | 1.39±0.69 | 1.38±0.68 | 1.41±0.71 | 0.746 |
| Stent area, mm² | | 6.34±2.01 | 6.48±2.24 | 6.22±1.81 | 0.305 |
| Neointima area, mm² | | 4.85±2.02 | 4.96±2.18 | 4.77±1.89 | 0.491 |
| Maximum neointima thickness, mm | | 1.03±0.31 | 1.06±0.33 | 1.01±0.29 | 0.185 |
| Distal reference area, mm² | | 4.62±2.06 | 4.64±2.09 | 4.60±2.04 | 0.894 |
| Proximal reference area, mm² | | 6.65±2.67 | 7.07±3.03 | 6.22±2.18 | 0.013 |
| Neointima characteristics at lesion | Neoatherosclerosis | 147 (47.0) | 147 (100.0) | – | |
| | Lipid neointima | 137 (43.8) | 137 (93.2) | – | |
| | Calcified neointima | 35 (11.2) | 35 (23.8) | – | |
| Neointima characteristics at MLA site | Neoatherosclerosis | 96 (35.6) | 96 (79.3) | 0 (0.0) | <0.001 |
| | Homogenous | 68 (25.2) | 8 (6.6) | 60 (40.3) | |
| | Heterogenous | 106 (39.3) | 17 (14.0) | 89 (59.7) | |
| Percentage of the frame with neoatherosclerosis, % | | – | 13.5 [7.5-27.6] | – | |
| Minimum FC thickness, µm | | – | 117.3±64.2 | – | |

## PREDICTORS FOR NEOATHEROSCLEROSIS

In univariate logistic regression analysis, age, eGFR and the time from PCI to ISR were significantly associated with neoatherosclerosis **(Table 4)**. Multivariate logistic regression analysis demonstrated that eGFR (OR 0.986, 95% CI: 0.974-0.998; p=0.023), the time from PCI to the ISR (OR 1.13, 95% CI: 1.06-1.22; p<0.001) and DES-ISR (OR 2.48, 95% CI: 1.18-5.43; p=0.019) were independent predictors for neoatherosclerosis **(Supplementary Table 1)**.

## CLINICAL OUTCOMES

The mean follow-up period was 828.4±417.3 days. A Kaplan-Meier analysis demonstrated that the freedom from CD-TLR rate at three years was significantly lower in lesions with neoatherosclerosis than in those without (58.3% [95% CI: 49.2%-69.0%] vs 70.4% [95% CI: 62.5%-79.4%], p=0.024) **(Figure 3)**. Multivariate analysis using the Cox proportional hazards model showed that neoatherosclerosis was an independent predictor of CD-TLR (HR 1.80, 95% CI: 1.15-2.82, p=0.011) **(Table 4, Supplementary Table 2)**. There was no significant difference in the incidence of all-cause death, cardiac death, and target vessel myocardial infarction between patients with and without neoatherosclerosis **(Supplementary Table 3)**.

Taking into account the effect of the treatment strategy on CD-TLR, we investigated the impact of neoatherosclerosis on the CD-TLR for each strategy. The freedom from CD-TLR rate at three years was significantly lower in the cases with neoatherosclerosis (62.0% [95% CI: 51.8-74.3%] vs 77.2% [95% CI: 67.9-87.8%],

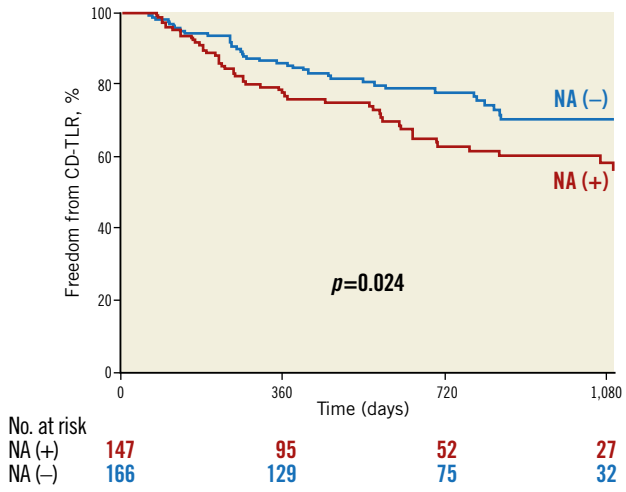


**Figure 3.** *Kaplan-Meier analysis. The freedom from CD-TLR rate at two years was significantly lower in lesions with neoatherosclerosis than in those without (62.9% [95% CI: 54.5-72.6%] vs 77.9% [95% CI: 71.3-85.1%], p=0.024).*

**Table 4. Multivariate analysis for predictors of CD-TLR in the entire cohort and DCB cohort.**

| Entire cohort | HR | 95% CI | *p*-value |
|---|---|---|---|
| Model 1 | 1.61 | 1.06-2.44 | 0.025 |
| Model 2 | 1.80 | 1.15-2.82 | 0.011 |
| Model 3 | 1.67 | 1.07-2.61 | 0.024 |
| Model 1: unadjusted. Model 2: adjusted for age, sex, smoking diabetes, eGFR, LDL cholesterol, type of previous stent, lesion length and final strategy. Model 3: Prentice, Williams and Peterson gap time (PWP-GT) model. | | | |
| **DCB cohort** | **HR** | **95% CI** | ***p*-value** |
| Model 1 | 2.11 | 1.17-3.79 | 0.012 |
| Model 2 | 2.22 | 1.19-4.16 | 0.013 |
| Model 3 | 1.99 | 1.04-3.81 | 0.037 |
| Model 1: unadjusted. Model 2: adjusted for age, sex, smoking, diabetes, eGFR, LDL cholesterol, lesion length and type of previous stent. Model 3: Prentice, Williams and Peterson gap time (PWP-GT) model. | | | |

p=0.011) **(Figure 4)** for the DCB cohort. It was lower in the cases with neoatherosclerosis for POBA (35.7% [95% CI: 20.0-63.6%] vs 65.0% [95% CI: 50.7-83.2%], p=0.040) **(Figure 4)**, while there was no significant difference for DES (68.0% [95% CI: 38.0-100.0%] vs 62.6% [95% CI: 42.3-92.7%], p=0.300) **(Figure 4)**. Similar to the entire cohort, in the DCB treatment group all multivariate models showed that neoatherosclerosis was an independent predictor of CD-TLR (HR 2.22, 95% CI: 1.19-4.16, p=0.013) **(Table 4)**.

Among lesions with neoatherosclerosis, there was no significant difference in the freedom from CD-TLR rate between lesions with lipid neointima, calcified neointima and both lipid and calcified neointima **(Supplementary Figure 1)**.

## Discussion

This multicentre study had the largest population to date with ISR analysed by OCT. Its major findings were as follows: (1) the frequency of neoatherosclerosis was around 50% in ISR lesions; (2) multivariate logistic regression analysis demonstrated that eGFR, the time from PCI to the ISR and DES-ISR were independent predictors for neoatherosclerosis; and (3) neoatherosclerosis was an independent predictor of a CD-TLR both in the entire cohort and in the DCB treatment group.

### FREQUENCY OF NEOATHEROSCLEROSIS

The evolution of DES, especially the introduction of newer-generation DES, has dramatically decreased the incidence of thrombotic

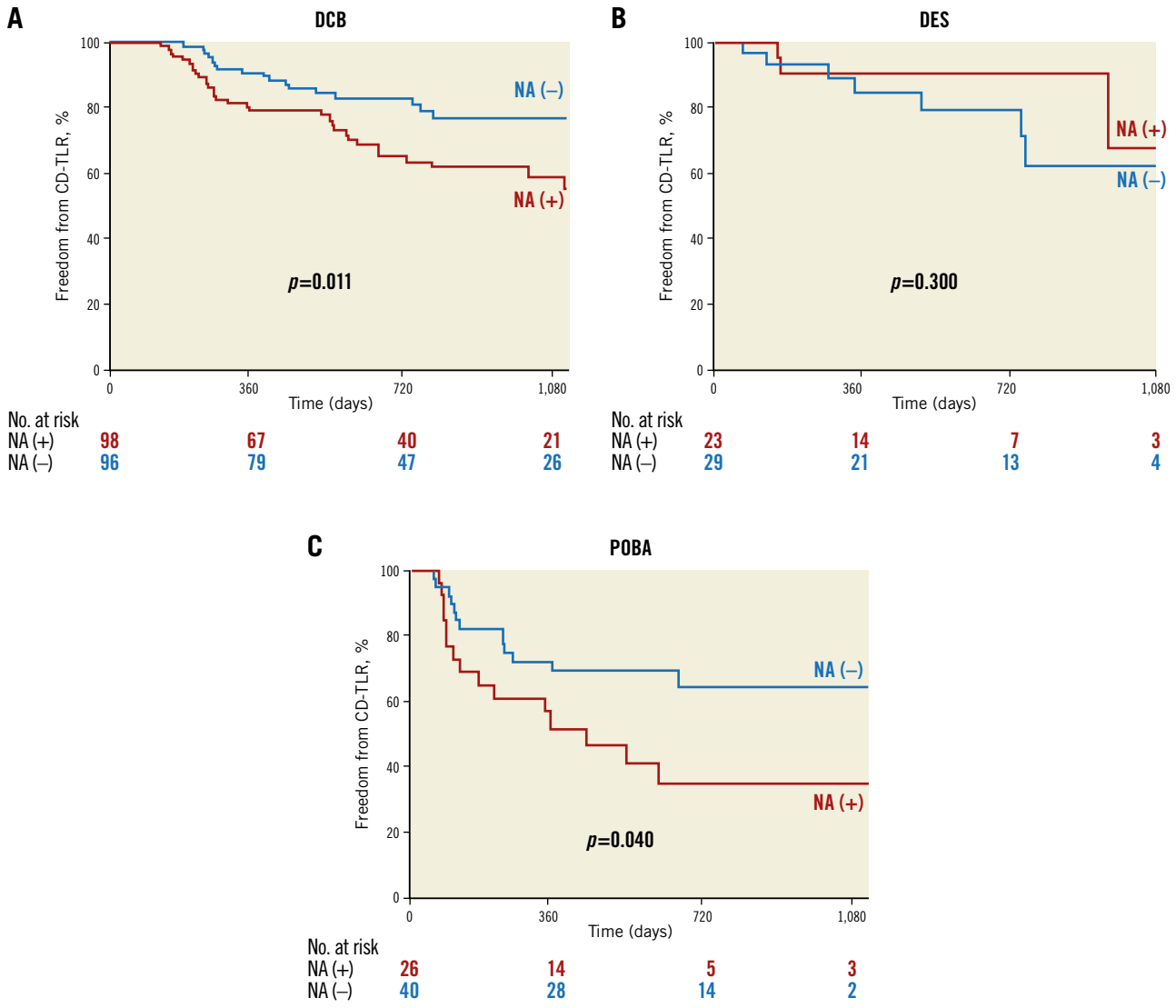


**Figure 4.** *Kaplan-Meier curves for clinically driven target lesion revascularisation (CD-TLR) in each treatment. A) Freedom from CD-TLR at three years was significantly lower in lesions with neoatherosclerosis than in those without in the DCB treatment group. B) There was no significant difference for DES. C) The freedom from CD-TLR rate at three years was lower in cases with neoatherosclerosis for the POBA treatment group.*

events due to improvements in drug concentration and polymer design, simultaneously with maintaining a low rate of restenosis. Nevertheless, late stent failure remains a concern even with the use of newer DES, since clinical trials have shown that there is an increase in the cumulative incidence of TLR over time in all generations of DES[12]. In fact, despite the better clinical outcomes with newer-generation durable polymer DES, a pathological study demonstrated that the frequency of neoatherosclerosis was similar between the newer- and first-generation DES[4]. Moreover, a pathological study showed that neoatherosclerosis was associated with ISR in both BMS and DES implantation[13], and it has been consistently correlated with late thrombotic events post stent implantation[13,14]. Yonetsu et al assessed 179 stents (mean duration 26.9 months, DES 59%) and reported OCT-detected neoatherosclerosis (lipid-laden neointima and/or calcification within the neointima) in 84 lesions (47%)[15]. Moreover. the prevalence of neoatherosclerosis in first-generation DES with restenosis beyond three years was 78% (7 of 9 lesions) at autopsy[16]. These results were compatible with the results of the current study.

### FACTORS ASSOCIATED WITH NEOATHEROSCLEROSIS

Multivariate logistic regression analysis demonstrated that eGFR, the time from PCI to the ISR and DES use were associated with neoatherosclerosis. Several OCT studies have shown that neoatherosclerosis occurs regardless of the type of stent and polymer and is more dependent on the vulnerable plaque under the stent[5]. One paper demonstrated that chronic kidney disease, a >70 mg/dL level of low-density cholesterol during the follow-up OCT, and the stent age were all independent predictors of neoatherosclerosis[17]. As possible mechanisms, previous studies have shown that oxidative stress and inflammation might mediate the observed high frequency of cardiovascular disease in patients with chronic kidney disease[18]. These mechanisms could also cause neoatherosclerotic changes in the stent.

In the present study, DES-ISR was associated more with neoatherosclerosis compared with BMS-ISR. This difference might be because of the difference in the mechanism of neoatherosclerosis between DES and BMS. In-stent neoatherosclerosis occurs in the years after stent implantation and more rapidly in DES when compared with BMS[5]. One histological paper demonstrated that accelerated neoatherosclerosis after DES implantation is probably a direct consequence of delayed vascular healing and inflammation caused by the antiproliferative drugs and polymers.

### IMPACT OF NEOATHEROSCLEROSIS ON CLINICAL OUTCOMES

Previous reports in relation to OCT in PCI have suggested that the ISR and TLR rates of lesions with a homogeneous structure were significantly higher in the POBA group than in the DCB and DES groups, whereas there were no differences in the ISR and TLR rates among the three groups in lesions with a heterogeneous structure[19]. There have been a few reports that have demonstrated the impact of neoatherosclerosis on clinical outcomes[5,6]. Kuroda et al demonstrated that neoatherosclerosis impacts on clinical outcome[6]. However, in that study, cases of neoatherosclerosis without ISR were enrolled and, moreover, PCI was not performed in any cases. The therapeutic strategy for ISR remains a challenge and there is no current consensus on how to treat ISR. However, finding an accurate diagnosis according to the characteristics of ISR is important for an appropriate therapy. The present findings might help to decide the strategy for ISR. Freedom from TLR after a DCB procedure was significantly lower in cases with neoatherosclerosis. Further improvement of DCB and DES is necessary for ISR treatment, especially for neoatherosclerosis.

## Limitations

First, this was a non-randomised observational study. Second, there were no serial OCT data at the time of stent implantation. Third, qualitative definitions of tissue structure and tissue backscatter have some limitations. Tissue structure and backscatter are influenced by intima thickness and the position of the OCT catheter relative to the vessel wall. Fourth, there are no control data of OCT imaging without restenosis in the stent. Fifth, small-sized balloons which were used to predilate lesions might have affected the OCT analysis, though the incidence of cases with predilatation before OCT imaging was 22.0%. Sixth, this study included only patients with ISR undergoing OCT-guided PCI; therefore, there was possible selection bias.

## Conclusions

In the multicentre ISR registry, OCT imaging demonstrated that eGFR, the time from PCI to the ISR and DES-ISR were independent predictors for neoatherosclerosis and that neoatherosclerosis in ISR lesions had a worse impact on the CD-TLR rate.

## Impact on daily practice

Despite better clinical outcomes with newer-generation durable polymer DES, a pathological study demonstrated that the frequency of neoatherosclerosis was similar between the newer- and first-generation DES. In this multicentre ISR registry, a multivariate logistic regression analysis demonstrated that eGFR, the time from PCI to the ISR and DES-ISR were independent predictors for neoatherosclerosis and multivariate regression analysis demonstrated that neoatherosclerosis was an independent predictor of CD-TLR. We should take into account additional strategies such as laser atherectomy. Also, further improvement of DCB and DES is probably necessary for the treatment of ISR.

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## Conflict of interest statement

The authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Appendix 1.** Quantitative coronary analyses.

**Supplementary Appendix 2.** OCT image acquisition.

**Supplementary Figure 1.** Kaplan-Meier analysis of CD-TLR in the different patterns of neoatherosclerosis.

**Supplementary Table 1.** Predictors for neoatherosclerosis.

**Supplementary Table 2.** Multivariate analysis for the predictors of CD-TLR in the entire cohort.

**Supplementary Table 3.** Differences in clinical outcomes.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00539*

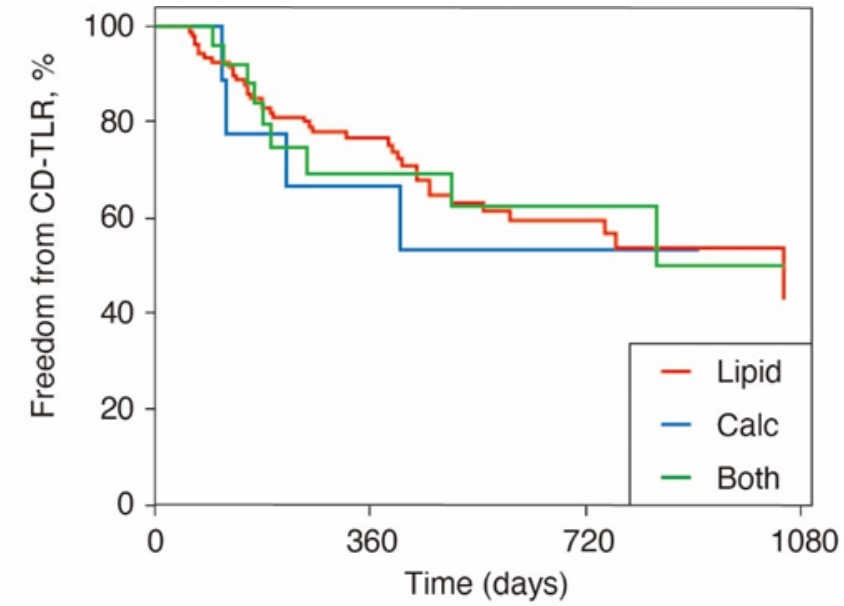
**Supplementary data**

**Supplementary Appendix 1. Quantitative coronary analyses**

After the administration of intracoronary nitroglycerine, angiography was performed during the PCI in at least two projections of the right coronary artery and at least four projections of the left coronary artery. The view showing the most severe stenosis was selected, and the reference diameter, minimal lumen diameter (MLD), percent diameter stenosis, and acute gain were measured by quantitative coronary angiography (QCA) (QAngio XA, version 7.1; Medis medical imaging systems, Leiden, the Netherlands).

**Supplementary Appendix 2. OCT image acquisition**

The OCT system used in this study consisted of a computer, monitor display, and interface unit (Model M2 Cardiology Imaging System; LightLab Imaging, Inc., Westford, MA, USA, or C7 OCT System; Abbott Vascular, Santa Clara, CA, USA). The patients received heparin intravenously before the OCT procedure. Using the M2 OCT system, an occlusion catheter (Helios; LightLab Imaging, Inc.) was used to remove blood. During the image acquisition, the occlusion balloon was inflated to 0.4-0.6 atmospheres, and Ringer's lactate was continuously infused at 0.3-0.5 ml/sec. The imaging catheter was pulled back from distal to proximal with a motorised system at 1.5 mm/s, and continuous images throughout the entire stent segment were digitally stored for subsequent analysis. Using the C7 OCT system, a conventional angioplasty guidewire (0.014-inch) was advanced distal to the region of interest, then the 2.7 Fr FD-OCT catheter (Dragonfly™; Abbott Vascular) was advanced over the guidewire beyond the region of interest. During the imaging acquisition, blood was displaced by an injection of iso-osmolar contrast dye. In general, in patients presenting with Thrombolysis In Myocardial Infarction (TIMI) flow grades 2 and 3, the OCT was performed before any intervention, while, for cases with a TIMI 0 or 1 flow, the OCT was performed after predilatation using only small-sized balloons. The images were calibrated by an automated adjustment of the Z-offset and the automated pullback was set at 20 mm/s. Data were acquired using a commercially available OCT system (C7 OCT System; Abbott Vascular) and were digitally stored.




| at risk | | | | |
|---|---|---|---|---|
| Lipid | 111 | 75 | 39 | 18 |
| Calc | 9 | 6 | 3 | 2 |
| Both | 26 | 13 | 9 | 6 |

**Supplementary Figure 1.** Kaplan-Meier analysis of CD-TLR in the different patterns of neoatherosclerosis.

**Supplementary Table 1. Predictors for neoatherosclerosis.**

| | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *p*-value | Adjusted odds ratio | 95% CI | *p*-value |
| Age | 1.026 | 1.001–1.051 | 0.042 | 1.03 | 0.999–1.069 | 0.064 |
| Sex | 0.93 | 0.53–1.63 | 0.802 | 1.16 | 0.55–2.49 | 0.693 |
| Hypertension | 1.16 | 0.63–2.15 | 0.630 | 1.13 | 0.52–2.47 | 0.756 |
| Smoking | 0.98 | 0.63–1.54 | 0.942 | 1.61 | 0.86–3.06 | 0.141 |
| HbA1c >7.0% | 1.37 | 0.81-2.32 | 0.243 | 1.39 | 0.71-2.75 | 0.338 |

| | | | | | | |
|---|---|---|---|---|---|---|
| eGFR, 1 mL/min/1.73 $m^2$ | 0.989 | 0.980–0.997 | <0.001 | 0.986 | 0.974–0.998 | 0.023 |
| LDL-C >70 mg/dl | 1.14 | 0.67–1.94 | 0.625 | 1.40 | 0.71–2.81 | 0.331 |
| DES as the stent type used | 1.50 | 0.86–2.65 | 0.160 | 2.48 | 1.18–5.43 | 0.019 |
| Time from PCI to ISR, years | 1.11 | 1.05–1.17 | <0.001 | 1.13 | 1.06–1.22 | <0.001 |
| Stent length | 1.00 | 0.99–1.01 | 0.982 | 0.98 | 0.96–1.00 | 0.105 |
| Neointimal thickness | 1.00 | 1.00–1.00 | 0.180 | 1.00 | 1.00–1.00 | 0.229 |

**Supplementary Table 2. Multivariate analysis for the predictors of CD-TLR in the entire cohort.**

| Model | HR | 95% CI | *p*-value | AIC | Harrell's C statistic |
|---|---|---|---|---|---|
| Model 1 | 1.61 | 1.06–2.44 | 0.025 | 945.938 | 0.560 |
| Model 2 | 1.63 | 1.07–2.48 | 0.022 | 945.110 | 0.594 |
| Model 3 | 1.75 | 1.12–2.73 | 0.014 | 860.082 | 0.667 |
| Model 4 | 1.73 | 1.11–2.70 | 0.016 | 863.246 | 0.665 |
| Model 5 | 1.65 | 1.08–2.52 | 0.020 | 910.335 | 0.691 |
| Model 6 | 1.70 | 1.11–2.60 | 0.015 | 895.205 | 0.705 |
| Model 7 | 1.90 | 1.21–2.97 | 0.005 | 839.307 | 0.719 |
| Model 8 | 1.71 | 1.10–2.66 | 0.018 | 854.877 | 0.673 |
| Model 9 | 1.79 | 1.15–2.81 | 0.011 | 830.335 | 0.738 |
| Model 10 | 1.89 | 1.20–2.96 | 0.006 | 840.001 | 0.727 |
| Model 11 | 1.80 | 1.15–2.82 | 0.011 | 833.919 | 0.737 |

Each hazard ratio is indicated for neoatherosclerosis in each model. Akaike's information criteria (AIC) was applied as an indicator for goodness of fit of each predictive model. The discrimination ability of models was calculated using Harrell's C statistic.

Model 1: unadjusted

Model 2: adjusted for age, sex

Model 3: adjusted for age, sex, eGFR and LDL cholesterol

Model 4: adjusted for age, sex, smoking, diabetes, eGFR and LDL cholesterol

Model 5: adjusted for age, sex, type of previous stent and final strategy

Model 6: adjusted for age, sex, type of previous stent, lesion length and final strategy

Model 7: adjusted for age, sex, eGFR, LDL cholesterol and final strategy

Model 8: adjusted for age, sex, eGFR, LDL cholesterol and type of previous stent

Model 9: adjusted for age, sex, eGFR, LDL cholesterol, type of previous stent, lesion length and final strategy

Model 10: adjusted for age, sex, smoking, diabetes, eGFR, LDL cholesterol, type of previous stent and final strategy

Model 11: adjusted for age, sex, smoking, diabetes, eGFR, LDL cholesterol, type of previous stent, lesion length and final strategy

**Supplementary Table 3. Differences in clinical outcomes.**

| | Neoatherosclerosis + | Neoatherosclerosis - | *p*-value |
|---|---|---|---|
| Event based on patients, N | 146 | 165 | |
| Death | 8 (5.5) | 10 (6.1) | >0.999 |
| Cardiac death | 2 (1.4) | 3 (1.8) | >0.999 |
| TV myocardial infarction | 3 (2.1) | 3 (1.8) | >0.999 |
| Event based on lesions, N | 147 | 166 | |
| CD-TLR | 51 (34.7) | 39 (23.5) | 0.039 |